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Re: **Docket No. 2005D-0062**; Draft Guidance for Industry on the Food and Drug Administration's "Drug Watch" for Emerging Drug Safety Information (Federal Register 24606 – 24607, Vol. 70, No. 89, Tuesday, May 10, 2005, Notices)

Dear Sir/Madam:

The following comments on the above-referenced draft guidance document on Drug Watch are submitted on behalf of Pfizer Inc. Pfizer discovers, develops, manufactures and markets leading prescription medicines for humans and animals and many of the world's best-known consumer health care brands. Our innovative, value-added products improve the quality of life of people around the world and help them enjoy longer, healthier and more productive lives. The company has three business segments: human health care, animal health care and consumer health care. Our products are available in more than 150 countries.

Health is our top priority at Pfizer, so we support any initiatives that improve the safe use of medicines. We believe that the dissemination of appropriate, understandable information about drugs is good for the public health; we want people, in consultation with their physicians, to make appropriate decisions about taking medicines and whether to stay on prescribed regimens; we want people to be able to benefit from modern medicines by understanding fully their potential therapeutic value and the risks they necessarily bring. Pfizer believes Drug Watch has the potential to serve the public's need in this regard – if done carefully.

We also believe that it is important that FDA make this effort toward increased communication more explicit in order to assuage public fears about the safety of its drug supply. Pfizer believes that FDA has for years faithfully and successfully executed the mandate of Congress to monitor and protect the safety of medicines. FDA's initiative to launch a high profile Drug Watch list may provide FDA the opportunity to let the public know what FDA currently does and what it has done for years. It is also an opportunity for the FDA to educate the public that all drugs have risks as well as benefits, just like

every activity in our daily lives, and that taking drugs requires tradeoffs. Conveying that message is very much in the public's interest.

Throughout the detailed comments to follow are some high level principles to which Pfizer believes FDA should adhere in order to optimize the public health benefit of Drug Watch, while minimizing its potential to do just the opposite. They may appear obvious, but they are so fundamental they bear repeating in the context of this new program.

First – and foremost – it is incumbent on FDA to be vigilant in protecting individuals, not just the safety of their drug supply. Safety includes honoring the sovereignty of individuals in making well-informed choices about whether or not to take a medicine, and their rights to have an unencumbered personal relationship with a physician to assist them in that task. In all matters related to Drug Watch, FDA must retain uncompromising attention to how elements of this new program will affect individual choices. FDA must be ever mindful that the person reading the web page is not an "average patient," but an individual with unique personal circumstances, varying capacity to comprehend, closely held beliefs and preferences, and the personal right to act as he or she sees fit on neutral, unbiased information. The population must never be mistaken for the individual; to add value, and to make drug use safer, Drug Watch must always defer to the individual.

Second, FDA must be mindful that it lacks the authority to mandate to doctors how they should practice medicine. The complex art of medicine in the context of biodiversity demands science, not conjecture. The diversity of our genes guarantees that people will react to drugs differently. Selection of therapeutic options should be made only within the bounds of the patient-physician relationship where that diversity is best known, and no proclamation on the Drug Watch web site should ever bias the critical decision-making that takes place within that relationship. Drug Watch should stick to facts – not speculate.

Third, since Drug Watch is meant to make drug use safer, it is important that there be clarity and precision regarding drug safety. In the questions and answers addendum to the draft guidance on Drug Watch, the response to Question 7 states: "FDA makes decisions about the safety of a particular drug after considering its benefits to treat a particular condition in relations to its risks. FDA therefore considers a drug safe when its benefits outweigh its risks for its intended use." This statement underscores a vitally important point: drug safety is not defined by potential or real risks; only the balance of risks within the context of benefits defines it. This principle should be an overarching theme of Drug Watch. Every communication to the public through Drug Watch should contain this balance of risk and benefit information, reminding of the benefits of the drug (its approved uses) as well as what may be its potential or emerging risk. Otherwise, patients may be unnecessarily frightened from taking needed medicines, the physician-patient relationship will be interfered with, the rights of the individual will be compromised, and Drug Watch will not improve drug safety.

These overarching principles guide Pfizer's assessment of the Drug Watch guidance. We have identified three major areas that deserve close attention in order for Drug Watch to

achieve its goal of safer drug use. Detailed comments are attached to this letter; here are brief, summary comments regarding each of those areas:

Processes

All stakeholders need to know how Drug Watch will work, how decisions will be made to post and withdraw drugs from the site under what time frames, where do the emerging risk data come from, who is to be held accountable, what are the website's checks and balances, etc. The success of Drug Watch will depend to a great extent on the degree to which the public trusts the FDA in protecting their interests through this endeavor. The processes must be well defined, explicit and inclusive, and the public must be assured that their concerns are met. Pfizer believes strongly that public confidence in Drug Watch also will be proportional to the involvement in the process by the practicing physician. Practicing physicians, not administrators or academics, should be given major responsibilities as consultants to FDA, especially on matters related to analysis and communication.

Pfizer further notes that omission of industry, as consultant to this process, is counter-productive if not dangerous. Since the stated goal of Drug Watch is to protect the public health by warning it about emerging or potential safety issues, it is prudent to use all possible resources available to the FDA, including those resources with the greatest possible insight and knowledge about a specific medicine. FDA should ensure an inclusionary process by inviting sponsors to fully participate in the Drug Watch initiative.

Analyses

In order to interpret Drug Watch information, patients, physicians, pharmacists and industry all need to know how and why a drug will be chosen for inclusion on the web site, and how and when it will be removed. The analysis of selection and de-selection of products for posting should be made explicit and vetted with the public. Included in this exposition should be a detailed explanation of the data and the evaluation techniques to be used: what will trigger a listing; what safety information will be used in the system; what are the safeguards that will be used to identify spurious data; etc.

Since data on adverse events come from a variety of sources with varying degrees of reliability, FDA should use data in its analyses that have been weighted according to reliability. When FDA reports to the public the sources of data for a Drug Watch listing, it should provide a link to another web page describing the reliability and importance FDA ascribes to the data it has used in its analyses. This issue has even more importance when FDA considers adverse event reports from nations with less sophisticated regulatory and pharmacovigilance standards.

Pfizer also recommends that FDA build evaluation measures into Drug Watch to determine how well the "emerging safety issue" communication system is actually working; for example, what is the percentage of false positives on the Drug Watch list and what has been the impact on the public. We also reiterate that since drug sponsors are in a position to know more than any other entity about their drugs, it is in the public's interest to have FDA consult with sponsors about emerging safety issues.

Communications

In developing this communication vehicle, the goal of informing the public of emerging risk information must be balanced with the need to avoid causing needless alarm. In an effort to provide the most up-to-date information on emerging data, specious inferences may be drawn and medicines may be falsely branded as "risky." This could unnecessarily alarm and confuse doctors and patients, discourage patients from taking needed medicines, and detract attention from the benefits of the medication and the risks of not taking it. It is important that physicians and consumers not focus on the absolute risk of a drug, but instead consider its benefit-risk balance and its relative risk compared to other drugs, and the underlying condition if left untreated. For each medicine on the Drug Watch web site, FDA should remind the public of its benefits as well as what might be its potential or emerging risks.

FDA needs to ensure that information communicated on the Drug Watch web site is clear and understandable. Literature on communicating risk to the public indicates that many persons are innumerate and cannot understand some of the basic mathematics used in risk concepts. FDA should use a panel of experts to identify a range of communication formats to optimize comprehension of its Drug Watch information over as broad a spectrum of the population as possible.

Pfizer strongly agrees with the Agency's stance that the listing of a drug on Drug Watch must not to be taken as an opportunity for a competitor manufacturer whose similar drug is not on Drug Watch to improve the marketing of its drug. FDA should enhance its vigilance on false advertising and promotion, implicit or explicit, and bring to bear against violators of this rule the full weight and force of its office. The rule should be stated emphatically in each listing of Drug Watch.

The substance of the above remarks reiterate Pfizer's strong commitment to the safe use of medicines, and endorsement of the underlying goal of FDA's initiative to improve risk communication to the public. We believe that Drug Watch, if correctly implemented, may represent an opportunity both to improve safety and to strengthen trust among the public. This initiative is very ambitious and it must be crafted carefully since it will be complex to implement in such a way that more people use drugs appropriately.

We thank FDA for the opportunity to comment on this draft guidance, and are pleased to respond to any questions the Agency may have about our comments.

Sincerely,

Gretchen S. Dieck

Gretchen S. Dieck

Detailed Comments

Processes

The processes that FDA opts to employ for communicating emerging risk information to the public are critically important for patients, caregivers and healthcare practitioners. Because the information posted on Drug Watch could have significant ramifications for patient health and safety, it is imperative that any standards and processes FDA adopts to implement Drug Watch be clear, consistent and well defined. Accordingly, we offer the following comments regarding suggested improvements in the processes set forth in the draft Guidance for Drug Watch:

Sponsor Involvement in the Decision to Post its Drug on Drug Watch

Pfizer believes that it is critical that a Sponsor be integrally involved in both the decision to post one of its drugs on Drug Watch and the specific language to be used in the posting. We fully recognize that the Agency wants to act quickly to disseminate information to healthcare providers and patients. However, because a Sponsor has the most knowledge about its products and the data for those products, Sponsors have an essential role to play regarding the dissemination of information regarding that product.

FDA correctly notes (footnote 4) that it regularly discusses information with Sponsors about the side effects of their drugs. To have and expect such discussions, but to then decline to provide Sponsors with the opportunity to play a role in an initiative such as Drug Watch, may serve to undercut the open exchange of information that FDA expects from regulated industry and may ultimately serve to deny doctors and consumers the best possible information about a posted product.

Sponsor Pre-Review of the Drug Watch Posting

Sponsor pre-review of the proposed FDA Drug Watch posting must also be addressed. Such review will be essential in helping to ensure that information posted on the website is accurate, thereby minimizing the posting of erroneous information. If FDA posts information in error, the ramifications for patients and prescribers can be significant - patients may stop taking medications on the basis of erroneous or incorrect information, prescribers may decide to cease prescribing the posted drug and/or tell their patients to stop taking the drug in question. Substantial damage to the public health, and to the public's confidence in Drug Watch, may occur if information is incorrectly posted. That damage might be impossible to undo with, e.g., a "corrective" posting, as it would be impossible for the Agency to ensure that such corrective posting would reach all of the consumers and prescribers who read and relied upon the erroneous information on the website. Accordingly, Pfizer requests that FDA explicitly provide for Sponsor pre-review of the posting.

Notification to and Involvement of the Sponsor

FDA must establish a process by which the Sponsor will be drawn into the discussion of the alleged safety issue. It is important for Sponsors to have full and timely access to the underlying information upon which FDA is considering posting so that they can evaluate that information, bring their own resources to bear upon it, and be ready to assist the FDA's on-going analysis, as appropriate.

To that end, the Guidance should specifically provide a Sponsor notification process that will include, among other things, provision of a copy of all information being considered by FDA, the source of the information, and any special analyses performed by FDA with respect to the issue.

Sponsors must be consulted at the time FDA is conducting its preliminary analysis, and given a defined period of time to provide any additional information that may help to clarify the potential safety concern. Sponsors' contributions could include such things as new adverse event reports or analyses that are still in the processing cycle, exposure information, or other perspectives that may contribute to an understanding of or resolution of the concern. This additional Sponsor perspective, if any, should be made available during the initial decision-making process, i.e., when the Drug Safety Oversight Board (DSOB) is considering the topic of concern. Further, FDA should give due consideration to any additional information about a drug provided by the Sponsors at any time during the period a drug is on Drug Watch to ensure that FDA uses all of the resources at its disposal and the most timely information is provided on Drug Watch.

The draft Guidance states that Sponsors will be notified "shortly before" the first instance in which information regarding their product is posted on the Drug Watch Web site (lines 216-218). As stated above, FDA needs to involve the Sponsor in the decision to post and the content of the posting, not just to "notify" it "shortly before" the posting.

Appealing the Decision to Post a Drug on Drug Watch

The Draft Guidance does not provide any process by which a Sponsor may appeal FDA's decision to post its drug on Drug Watch, nor does the Draft Guidance provide a process by which a Sponsor may propose alternative wording for the site posting. Critical to the integrity of the process is the establishment of a mechanism enabling the Sponsor to request DSOB review, and withdrawal or rewording of the posted information. Such appeal would, of course, need to be based upon definitive, established criteria that could demonstrate that the posting was inaccurate or otherwise lacking a credible basis.

Linking a Product Drug Watch Posting to the Product Prescribing Information

As discussed elsewhere in these comments, Pfizer believes it is essential that any Drug Watch posting contain not only information about emerging "risks" for a drug product, but also the known benefits of the product. Only where benefits and risks are linked can healthcare prescribers and consumers obtain the full information about the product and

make informed decisions about the appropriate course of action for a given patient in light of the "emerging" information. Accordingly, each posting on Drug Watch should also contain a link to the drug product label. The product label is, and must remain, the most definitive source of information about a drug product.

Creation of a Process for Updating the Website

In the draft Guidance, FDA states that it intends to work "as quickly as possible to assess and address the potential safety issues..." (lines 37-38), and that it intends to update information on the Drug Watch frequently (lines 130-131). The Guidance should include the establishment of a process regarding the nature and frequency of the updating process, including minimum cycle times for updating the site, the procedures to be used to resolve an issue, and the establishment of an "archive" that demonstrates the evolution of emerging information for each posted product over time.

In addition, we suggest that the Drug Watch posting include information regarding the steps the Agency is taking to assess and address each emerging safety issue, and the estimated timeframe for completion of this assessment. In the interest of the public health, the single entity with the most knowledge about a given drug, the drug's Sponsor, should be included in all proceedings on updating and removal of products from the site. There should be a specific mechanism established by a which a Sponsor, or other entity, can request an update to the web site based on the receipt of further information or further evaluation of the issue.

In some instances, FDA's further evaluation of emerging safety information may find a causal relationship between a drug and an adverse event and may identify information that could have an impact on the prescribing of a drug (e.g., the identified adverse event affects only a specific patient population). In such cases, the confirmed risk information should be incorporated into the drug's label; information posted on Drug Watch should not supplant the information contained in the drug label. FDA should ensure that the Drug Watch posting is updated to reflect regulatory action (e.g., drug label is changed).

The Draft Guidance must set forth the processes by which the Website will be updated, particularly where a purported safety issue has been "resolved," including a determination that no causal relationship has been found. Documenting resolution of a posted issue is an important aspect of the process that will reassure the public that issues have been adequately addressed. This in turn will help to instill greater confidence in the program. Therefore, it is important that a product be removed from the Drug Watch in a timely manner and the rationale for its removal be provided on the website. Information regarding product removal from the site should be accorded the same level of highlighting and publicity that the original posting received. Information regarding the product removal should remain on the web site for a period of time that is sufficient to assuage public fears about the drug, perhaps 12 months. We also recommend that the Agency develop and maintain a permanent on-line reference for each issue that is posted to the Drug Watch, including how it was evaluated, and its resolution.

The Drug Safety Oversight Board

In lines 173-203, FDA sets forth the representation of the Drug Safety Oversight Board ("DSOB"). The Board contains representatives from CDER, CBER, CDRH, and other Department of Health and Human Services Offices. The draft Guidance also permits the DSOB to consult with the FDA Advisory Committee Chairs, other external scientific experts and consumer and patient representatives. Conspicuously absent from the list is any form of industry representation.

We believe it is critical that FDA formally include regulated industry on the list of *potential* consultants to the DSOB. Because the pharmaceutical industry, in general, and drug Sponsors, in particular, have extensive knowledge about the products they market and the diseases they treat, it is important that industry be recognized as a potentially valuable resource for the DSOB. To decline to permit industry participation in the process would ultimately serve to undercut Drug Watch by eliminating a critical source of extensive information about the product, disease state, epidemiologic information etc. This would not be consistent with FDA's avowed purpose of providing the public with access to "the most up-to-date and emerging product information ..." (lines 60-61).

Establishing a Process for Initial and On-Going Analysis of Physician And Patient Response to Drug Watch

It is critical that, prior to launching Drug Watch, FDA develop a process to determine:

a. The most effective means of communicating emerging safety information to physicians and consumers from both a content and format perspective; and

b. How physicians and consumers will likely respond to emerging safety information posted on the website.

Because Drug Watch represents a radical departure from prior Agency policy, i.e., providing *emerging* safety information to the public, FDA must proceed in a measured and considered way and assess how best to communicate such information to optimize public response. (See Section below re: Communicating Risks). It is important that FDA understand how the public is likely to respond to information posted on Drug Watch before launching this new policy. FDA should revise and refine the Drug Watch program on the basis of the findings of these analyses.

Analyses

Background

FDA states: "Our goal with the Drug Watch is to share emerging safety information before we have fully determined its significance or taken final regulatory action so that patients and healthcare professionals will have the most current information concerning the potential risks and benefits of a marketed drug product upon which to make individual treatment decisions" (lines 64-68). In other sections of our response to this Drug Watch draft guidance we have noted that reporting unsubstantiated, "emerging" safety issues to the public has the potential to do harm as well as good, harm arising when patients are unnecessarily frightened away from taking needed medicines. How FDA defines terms, selects data and uses analyses both for listing and de-listing is integral to ensuring a beneficial process while avoiding harm.

Defining and Using Terms Appropriately

If FDA is still analyzing information while posting it, not yet having reached a conclusion about a drug's safety, we do not think it realistic to expect that patients or even healthcare providers will be able to make proper sense of the situation either. This is particularly acute for most patients who are likely not to have understanding of pharmacology of medicines. It is critical, therefore, for FDA to clearly define what it means by "a significant emerging safety issue."

We recommend that FDA be cautious in its use of the term "signal" to represent an emerging safety issue, as in: "... when FDA has determined that, despite the initial signals, there is no new safety concern" (lines 211-212). A handful of adverse events reports do not constitute a "signal;" it could be background noise. The use of the term could confuse people, since most of the public will not know what a "signal" is in the context of drug safety. Use of the term "signal" on Drug Watch also would be a false representation of what is being posted. Until a drug-injury event is confirmed, it would be safer for the public to call data posted on Drug Watch "reports."

The Drug Watch guidance states that Drug Watch will provide information about drugs with "significant" emerging safety issues (line 76), but other parts of the document (lines 33, 34, 35, 64, 65, 93, 94, 120-124) indicate that the aim of the program is in part to determine if emerging safety concerns are, in fact, significant at all. The ultimate aim of Drug Watch is to determine whether an emerging issue posted on Drug Watch is statistically or medically significant; the significance of an emerging issue is not known at the time of posting. Hence, the term "significant" can be confusing in this context and we recommend that it not be used where an issue may be "emerging."

Terms that will be used in analyses, both preliminary and follow-up, should be clearly defined so they are usable and understandable by all stakeholders. We suggest further guidance on Drug Watch clarify what is meant by terms describing analyses, such as "emerging" (line 19), "actively evaluating" and "early" (line 22), "causal relationship"

(line 86), "adverse events" (line 87), and "risk/benefit assessment" (line 88). We strongly recommend that terms be defined clearly in a well-written glossary, with a link to it on each posting on the Drug Watch website. We suggest links to a glossary (as well as links to descriptions of data and analytical techniques) in order to both better inform stakeholders seeking such information and avoid overwhelming and confusing users who have more limited capacities to comprehend Drug Watch information and messages.

The Drug Watch Disclaimer

Pfizer believes the proposed FDA disclaimer is insufficient: "This information reflects FDA's preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about, this information. FDA intends to update this web page when additional information or analyses become available" (lines 121-124). We suggest the disclaimer be expanded to include a statement saying that neither a scientific association or a causal relationship has been established, and the validity of the information is subject to verification, but that rather in an abundance of caution this information is being shared. The statement should also include the fact that sometimes these emerging reports do not lead to any risk finding. Further, the disclaimer should specifically state that the information is not yet considered sufficient to warrant a change in the product's prescribing information (its label). We recommend FDA precede this information with direct communications to patients about discussing their use of the drug with their doctor (described in detail in the following section on communications) so that they may consider the patient's particular circumstances, and what the benefits and risks of the medication might be for that patient.

Criteria for Posting on Drug Watch

There are discrepancies throughout the Drug Watch draft guidance with respect to the nature of the safety issues FDA intends to address on Drug Watch and the standards FDA intends to apply in determining whether to post a product on the site. The criteria for posting information on the Drug Watch must be more explicitly defined. This is particularly important because the information will be posted "before (FDA) has fully determined its significance" (line 65). Given the risk of premature and/or inaccurate posting of information that could lead to confusion among healthcare providers, patients, and other regulators, it is crucial to have clearly defined parameters for the selection of products and information to be posted.

The first listed criterion, "Whether new and emerging safety information could significantly affect prescribing decisions or how patients should be monitored" (lines 153-157) is vague with regard to the strength of the information necessary to make such a determination (e.g. number of cases needed and robustness of reports). We recommend the guidance also specify the criteria used in determining that "an unapproved (off-label) use of the drug appears to pose a significant risk to patients" (lines 162-163). FDA should further clarify how products with widespread off-label usage fit into this category.

It is unclear whether the Drug Watch postings will be limited to only emerging safety issues that would be considered "serious" pursuant to 21 C.F.R. §314.80 or whether "non-serious adverse events" could be subject to posting. This issue requires clarification.

FDA notes (lines 167-168) that before posting information on Drug Watch, the Agency will conduct a "...preliminary analysis to determine that the new safety information is sufficiently credible..." Absent from the draft Guidance, however, is any indication as to what might constitute a "preliminary analysis" and what thresholds or criteria would be deemed to be "sufficiently credible." This issue also requires clarification.

The confusion in standards and definitional criteria is evidenced in the examples of potential postings FDA provides in the draft Guidance. There is an inconsistency between the general inclusion criteria for Drug Watch, i.e., "emerging safety information," and the examples provided in this section (lines 83-110), particularly examples B and C. These examples discuss risks for which conclusions appear to have been established, not which are "emerging."

Risk management action plans (example C), or RiskMAPs, especially do not belong on Drug Watch. RiskMAPS are used in cases where the drug-injury event is well specified (and not "emerging"), and FDA and the Sponsor has decided on a course of action to manage risks. Because the information supporting RiskMAPs is so well developed, posting a RiskMAP on Drug Watch - a list meant to describe unsubstantiated safety issues – would only serve to diminish the RiskMAP's impact.

FDA should vet with the public transparent analysis plans that detail the events to be included and the methodologies that will be used to select those events for posting. Detail should be sufficient to allow the patients, non-healthcare professionals and healthcare providers the ability to use the information appropriately if they so wish. After posting a drug, FDA should make careful use of the best available "data mining" techniques and other analytic paradigms in order to rapidly uncover real "signals" or identify false ones.

Weighting Evidence

In addition to concerns regarding the lack of specificity on the standards, discussed above, Pfizer believes that is essential that FDA be explicit about the strength of the information necessary to make a determination to post. Absent from the draft Guidance is any reference, for example, to the number of reports or data sources necessary to trigger inclusion on Drug Watch and/or the robustness of the reports. Certainly reports from treating physicians should be accorded more weight and "validity" than anecdotal reports from non-treating healthcare professionals or sales representatives from competitor companies. Lawsuits themselves are often adverse drug event reports, and these should be afforded very little weight. The FDA Guidance Document must provide detail regarding its intended approach to the weighting of the evidence to ensure consistency and transparency in the analytical process.

We additionally recommend that each Drug Watch listing include a link to a description of potential data sources, ranked from most to least valid, with adequate explanation of their potential shortcomings. This will help to add transparency to the process and may assist healthcare practitioners in understanding the nature of the emerging safety issue.

Quality Control

FDA should monitor and evaluate the accuracy of postings with respect to the number and percent of "false positives" – those postings for which drug-injury causation was not found. These evaluations will inform FDA how to improve data selection, weighting and analyses.

Communications

Background

In response to calls for earlier warnings of possible drug safety issues, "FDA has concluded it should do more to make drug information available as it emerges while the Agency is evaluating its significance" (lines 59-60). This is clearly a double-edged sword: communicating unsubstantiated reports of possible drug safety issues to the public has the potential to do harm as well as good. The analytical complexities of identifying emerging safety issues are discussed in detail above. A benefit of earlier reporting may be realized when the reports presage accurately a real causal relationship. Getting patients to talk with a doctor earlier about whether a medicine is appropriate for them, given a reassessment of the benefit-risk balance in light of the new information, could save pain, suffering and lives. The downside of reporting unsubstantiated data happens when two conditions occur at the same time: when the reports are false positives (when they do not represent a real drug-injury relationship) and when people have, on the basis of the reports, stopped taking a needed medicine, incurring unnecessary pain, suffering, and in some cases, premature death. As in all activities, Drug Watch must balance potential benefits with potential risks, alerting doctors and patients appropriately while avoiding frightening patients and confusing doctors' practice of medicine. Accurate, appropriate and effective communication is essential to the success of Drug Watch. The following remarks address Drug Watch communications topics pertinent to the major stakeholders: patients, doctors, sponsors and the FDA.

Communicating Risks

There has been much research in the past 40 years about how persons evaluate risks, leading to a growing body of empirical evidence about the use of cognitive skills in assessing risk, the use of heuristics (i.e., mental shortcuts) when risk concepts tax those skills, the biases those heuristics have on risk perceptions, and our abilities to understand risk concepts and communications. There is still much uncertainty, however, about how individuals personally characterize risks, how best to communicate risks to the public, and whether and how persons understand risk concepts and communication. We strongly recommend that, given the importance of risk communications in Drug Watch and the risks of giving confusing and possibly harmful information to the public, FDA seek the advice and counsel of experts in risk communication, researchers in cognitive psychology and practicing physicians about how to report emerging risks on the public web site.

Recent models of cognition[1] propose that persons rely on two distinct cognitive skills in making decisions: reasoning and intuition. Reasoning is slow, deliberate and effortful; intuition is fast and effortless. Persons typically rely on their intuition when making decisions, monitoring those decisions with reasoning. However, since cognitive capacity

[1] Kahneman, Daniel, Maps of Bounded Rationality: Psychology for Behavioral Economic, The American Economic Review, Vol. 93, No. 5, December 2003.

is limited by elements such as time pressures, amount of information or complexity of information, we are often lax in our reasoning, resulting in errors in judgment. Given low health literacy rates and general innumeracy of a large proportion of the population, risk concepts are particularly difficult to understand, even more so under time pressures and complexity typically present in medical care situations. Under such circumstances, many people use mental shortcuts to try to understand difficult risk concepts, relying on a wide range of heuristics that color or bias perceptions of risk.[2,3,4,5,6] Perceptions of risk also are affected, and can be manipulated, by how the risks are presented, including how concepts are framed and whether context is provided. Since persons responsible for communicating risks have the ability to manipulate perceptions and behavior, those persons must examine closely the ethical implications of their risk-information program. The Drug Watch initiative places FDA squarely in the position of potentially scaring persons away from taking needed medicines: "Merely mentioning possible adverse consequences (no matter how rare) of some product or activity could enhance their perceived likelihood and make them appear more frightening."[7]

Innumeracy among the public makes communication of risk especially difficult, so alternatives to written documentation such as graphics and other visual representations to enhance the public's understanding of risk have been proposed.[8] Unfortunately, there is still much uncertainty as to the impact of visuals on comprehension, and the future research agenda in this area remains robust.[9] One recent study of the impact of visuals on comprehension and motivation suggests that the actual use of information increases when cognitive effort is reduced, when the decision-maker is moved closer to the actual experience, and when the meaning of information is highlighted for the decision-maker.[10] This research also highlights the importance of experience, skill and motivation of users, suggesting the need for an array of information-presentation formats to optimize comprehension by users. Very recent research has reaffirmed the role of the heuristic of "affect," or feeling (like-dislike, approach-avoid, etc.), at the core of decision-making, suggesting that an appeal to affect in information-presentation formats may be very

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[2] Covello, Vincent T., Detlof von Winterfeldt and Paul Slovic, Risk Communication: A Review of the Literature, Risk Abstracts, 3, 171-182. October 1986.
[3] Fischoff, Baruch, Ann Bostrom and Marilyn Jacobs Quadrel, Risk Perception and Communication, in Detels, R., McEwen, J., Beaglehole, R. & Tanaka, H., Oxford Textbook of Public Health, 4th ed. Oxford University Press, 2002.
[4] Slovic, Paul, The Perception of Risk, Earthscan Publications Ltd., 2000
[5] Heuristics and Biases, The Psychology of Intuitive Judgment, Gilovich, Thomas, Dale Griffin and Daniel Kahneman, eds. Cambridge University Press, 2002.
[6] Slovic, Paul, Ellen Peters, Gretchen Dieck, Susan Berger and John Grana, Risk Perception of Prescription Drugs, Results of a National Survey; (in review, Risk Analysis)
[7] Slovic, Paul, Informing and Educating the Public About Risk, Risk Analysis, Vol. 6, No. 4, 1986.
[8] Peters, Ellen, Daniel Vastfjall, Paul Slovic, C.K. Mertz, Ketti Mazzocco and Stephan Dickert, Numeracy and Decision Making, in press, Psychological Science.
[9] Lipkus, Isaac M., J. G. Hollands, The Visual Communication of Risk, Journal of the National Cancer Institute Monographs No. 25, 1999.
[10] Hibbard, Judith H. and Ellen Peters, Supporting Informed Consumer Health Care Decisions: Data Presentation Approaches that Facilitate the Use of Information in Choice, Annual review of Public Health, 2003, 24:413-33.

helpful in therapeutic contexts.[11] The ethical implications of the manipulations of affect are obvious. Recent dramatic progress of biomedical science has increased both the quantity and quality of new drugs, making the communication of their risks and benefits even more challenging and critical, drawing the focus of the Agency for Healthcare Research and Quality.[12] Potential solutions have been outlined, including enhanced education of health care providers, increased motivation of patients and families, use of creative communication technologies, and better organization of and access to medical records and information.

This brief overview of risk evaluation and communication research is not meant to be exhaustive; rather, it is a cautionary statement of the complexity and criticality of conveying unsubstantiated, emerging safety data to the public. We reiterate our recommendation for FDA to consult with experts in the field of risk communication, cognitive psychologists and practicing physicians before launching this aggressive program, in order to avoid the potential untoward impacts of confusing or faulty communication.

Communicating the Benefit-Risk Balance

FDA states that it is making information on emerging safety issues available "... so that patients and healthcare professionals will have the most current information concerning the potential risks and benefits of a marketed drug ..." (lines 66-67). We heartily agree with the sentiment that the benefits as well as risks of a drug should be included on each listing of Drug Watch; unfortunately, the guidance does not address this issue.

In the questions and answers addendum to the guidance, FDA states the following: "FDA makes decisions about the safety of a particular drug after considering its benefit to treat a particular condition in relation to its risks. FDA therefore considers a drug safe when its benefits outweigh its risks for its intended use" (question 7). As this statement indicates, drug safety is not defined by a medicine's potential or real risks, but rather by the balance of risks and benefits characterizing it. Another critical consideration in drug safety is the acknowledgement that all drugs pose risks, as does the choice not to take a needed medicine. Consequently, physicians and consumers must focus *not* on the absolute risk of the drug, but on its benefit-risk balance and to the underlying disease, if left untreated. Communication of these fundamental truths about drug safety is crucial, and they should be an overarching theme of Drug Watch. Each and every communication to the public through Drug Watch should contain this balance of risk and benefit information, reminding what the drug is used for in the first place as well as what may be its potential or emerging risks. Drug Watch must be designed to report on safety, not risk. Otherwise, with a sole focus on risks, patients may be unnecessarily frightened

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[11] E. Peters, (in press) "The functions of affect in the construction of preferences," in S. Lichtenstein & P. Slovic (Eds.), The Construction of Preference, Cambridge University Press.
[12] Campbell, William H. and Robert M. Califf, Improving communication of drug risks to prevent patient injury: proceedings of a workshop, Pharmacoepidemiology and Drug Safety 2003; 12: 183-194.

from taking needed medicines, the physician-patient relationship will be interfered with, and Drug Watch will not promote the safe use of medicines.

It is also critical to keep in mind that because of unique biological makeup and specific environmental circumstances, individuals will respond differently to a given drug. As a result, a medicine's benefit-risk balance and relative risk will be different for individual patients. Presenting both benefit and risk information will enable physicians and patients to make a balanced decision that is best for an individual patient. Drug Watch should also provide contextual information that will enable physicians to decipher how the emerging safety information likely impacts the benefit-risk balance for a specific patient.

Communicating Results of Evaluation of Emerging Information

FDA also must consider what information would be provided once it has completed its analysis of an emerging safety risk. In instances where it is concluded that there is no link between emerging risk information and a specific drug, FDA must ensure that this finding is communicated clearly and quickly so that physicians do not alter their prescribing practices needlessly, potentially putting their patients at great risk. FDA must also determine whether to remove the drug from the Drug Watch.

For the public health, communicating removal of a drug from the Drug Watch list can be as important as posting one, since persons who have stopped taking a needed drug after it is listed on Drug Watch may be suffering needlessly or are at higher risk of experiencing the consequences of their underlying disease. Trying to discredit claims after making them familiar to older adults also may sometimes backfire, increasing their tendency to call those claims true.[13] We recommend, where appropriate, that FDA make it absolutely clear on the Drug Watch web site that, after further analysis, there is no safety problem and the drug is safe, or that the drug was not found to be unsafe. Also, where appropriate, FDA should make it clear that the issue has been resolved and a change has been made to prescribing instructions (the label), and that these new instructions should be discussed with the prescribing physician. These messages should be highlighted on the Drug Watch central page, with attention-focusing graphics that announce "New Information About Drug X." And, of course, patient and physician information sheets should be revised immediately.

We recommend that information on the removal of a drug from Drug Watch should remain on the public web site for a length of time sufficient to assuage public fears, perhaps a year. A link should be included that describes all decisions about a drug that is posted on Drug Watch. This is important for liability concerns, too, to prevent the unnecessary medical costs of spurious litigation.

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[13] Skurnik, Ian, Carolyn Yoon, Denise C. Park and Norbert Schwarz, How Warnings About False Claims Become Recommendations, Journal of Consumer Research, March 2005.

Avoiding Unintended Consequences

The Drug Watch website has the potential to dramatically alter FDA's drug safety communication to physicians and patients. To ensure that Drug Watch is used as a tool to benefit, rather than hurt, public health, however, FDA must promote judicious and appropriate use of the website information. To this end, FDA should be thoughtful and cautious in disseminating emerging safety information, and it should partner with physicians, patients, drug sponsors and the general public to ensure that Drug Watch is used to benefit patients and advance our knowledge of medicines.

Overreaction to Drug Risks

Several unintended consequences could undermine the effectiveness of Drug Watch and potentially threaten patient health. For example, physicians may overreact to the emerging risk information on Drug Watch and become overly-cautions in prescribing drugs listed on Drug Watch. Similarly, some physicians might opt to discontinue all of their patients from a drug posted on Drug Watch. Excessive caution could result from a number of factors including physicians' lack of understanding of the preliminary nature of the safety information on Drug Watch or a conscious decision to practice "defensive medicine" to minimize potential malpractice suits. Physician overreaction could have major deleterious consequences for patients if they are needlessly switched to alternative medications, which may be less effective or have more serious side effects for them, or if the physician discontinues treatment because no other alternative to the drug exists. In such instances, a patient may be denied access to appropriate medical care.

Undermining of the Physician-Patient Relationship

Another unintended consequence could be an undermining of trust in physicians if they are not armed with sufficient information to answer patients' questions on potential safety concerns posted on Drug Watch. Alternatively, physicians' credibility may be questioned if they are unable to communicate effectively to their patients why they should continue treatment with a medicine listed on Drug Watch. Both situations could harm the doctor-patient relationship. These situations may also lead to patients deciding unilaterally to discontinue a needed treatment despite the advice of their physician. The consequences of such a decision could be dire since discontinuing a needed medicine may pose a much greater risk to the health of the patient than would exposure to a drug's potential side effects.

Increased Liability for Physicians

Another inadvertent effect could be increased liability for the physician arising from a new responsibility to monitor and be conversant in the most current information posted on Drug Watch. Given the increasing demands on their time due to managed care pressures and rapid pace of medical advances, physicians likely will find it exceedingly challenging to keep abreast of the latest postings on Drug Watch and to translate how the

information is relevant for individual patients. The ambiguity of the information on Drug Watch likely will expose physicians to increased liability, even in instances where no causal link can be established between a drug and an adverse event. FDA should consider how it might dissuade third parties from misusing Drug Watch to file frivolous lawsuits.

Inhibition of Clinical Trial Enrollment

A fourth inadvertent effect may be the impact of Drug Watch on clinical trial enrollment: Risk information posted on a website could have a negative impact on ongoing clinical trials as it may cause unnecessary concern to clinical investigators and patients. Specifically, it may prejudice physicians against recommending their patients for a clinical trial of a drug listed on Drug Watch or it may cause trial participants to withdraw their consent despite the counsel of their physician or the clinical trial investigator. Also, clinical investigators might be discouraged from participating in clinical trials because of liability or other concerns. This would be an unfortunate consequence given the preliminary nature of the information posted on Drug Watch, coupled with the challenges clinical trial sponsors face in identifying appropriate enrollees for the trials. Highlighting emerging risks also may cause physicians and patients to overemphasize all drugs' risks relative to their benefits, and thus deter persons from involvement in clinical trials of any drug. Further confusion to patients and investigators could ensue if drug sponsors are required to update investigator brochures each and every instance of a change in status of a drug on Drug Watch. Any activity that would discourage clinical trial enrollment based on unwarranted safety concerns would do a great disservice to the continued development of new life-saving medicines.

Communication to Patients and Consumers

Clarity of Language

FDA states "... listing of a drug on the Drug Watch should not be construed as a statement by the FDA that the drug is dangerous ..." (lines 24-25). We concur, but ask what steps can be taken to ensure that such interpretation does not occur. We recommend that FDA make a clear and bolded statement on each Drug Watch posting using exactly that statement about not misconstruing a listing, with an additional statement that persons using the posted drug should not rush to judgment and discontinue their medication without discussing the use of the drug with their doctor.

FDA states: "Our goal with the Drug Watch is to share emerging safety information before we have fully determined its significance or taken final regulatory action so that patients and healthcare professionals will have the most current information concerning the potential risks and benefits of a marketed drug product upon which to make individual treatment decisions" (lines 64-68). If FDA is still analyzing information while posting it, not yet having reached a conclusion about a drug's safety, we do not think it realistic to expect that patients or even healthcare providers will be able to make proper sense of the situation either. This situation is particularly acute for most patients who are

likely not to have understanding of pharmacology or medicine. It is important, therefore, that language for each posting contain facts only, not hypotheses (such as possible mechanisms of action). Such facts should include more context about the emerging safety issue, such as number of reports, the source of those reports in light of the validity of various sources (described above), specific effects on persons with what conditions, etc.

FDA states as an example posting: "FDA is investigating post marketing reports of renal failure in elderly patients treated with Drug A, but a causal relationship has not been established. We are continuing to analyze these reports to determine whether the occurrence of these adverse events affect the risk/benefit assessment of Drug A therapy" (85-88). It is not likely that the patients would understand this sophisticated language. In these brief lines, there are many words or phrases many would not comprehend or even recognize: "post marketing;" "renal;" "causal relationship;" "adverse events;" and "risk/benefit assessment." Language in Drug Watch needs to be written with clarity for comprehension; caution should be taken not to include language hinting at complex statistical relationships (since by the definition of Drug Watch, there are none at the time of the drug posting), or "legalese" language meant to protect the Agency if it errs; the public's health is too important.

Similarly in a second example: "Drug B has been associated with serious skin reactions in patients allergic to eggs (line 100)." The phrase "... has been associated with ..." is not one the public in general will understand. Language must be simplified. In a case like this, something like the following language could be used: "Some people with allergies to eggs have experienced serious skin reactions such as XXX when taking Drug B." To the extent that complex concepts must be presented on a Drug Watch listing, we recommend that each Drug Watch web posting include a link to a well-written, understandable glossary of terms.

Communicating to the Individual

The "average patient" does not exist, so communications from Drug Watch should be crafted carefully to speak to the individual. FDA must be ever mindful that the person reading the Drug Watch web page is not an "average patient," but an individual with unique biological dispositions, varying capacity to comprehend, closely held sovereign beliefs and preferences, and the personal right to act as he or she sees fit on neutral, unbiased information.

We recommend two key principles for Drug Watch to ensure the individual is addressed. First, and foremost, since selection of therapeutic options should be made only within the bounds of the patient-physician relationship where individual biodiversity is best known, Drug Watch should strongly encourage persons affected by a listing of a drug on drug watch to discuss their use of the drug with their physicians. Second, information about an emerging safety issue must contain as much specific data as possible about the persons who have been affected, such as age, gender, locale, whether there were concomitant conditions, whether drug-drug interactions were present, etc. For example, the statement,

"... renal failure in elderly patients ..." (line 85) is insufficient. Specificity will help persons identify whether they personally may be at risk, and will serve to assuage unnecessary fears in those who do not meet the profile. Contextual information is absolutely critical to the safety of persons viewing Drug Watch. We reiterate: Drug Watch should contain no hypotheses that might frighten persons away from taking needed medicines; only facts that help persons relate appropriately to the information.

Drug Watch also should be prepared to meet the needs of individuals for additional information. It is likely that persons affected by a Drug Watch listing (or their physicians) will seek further information from providers, sponsors and FDA. We recommend that for each drug listed on Drug Watch the FDA fund a "hot line" to answer patient questions. FDA also should designate in-house rapporteurs for each listing to communicate effectively with concerned patients and physicians. Drug Watch should contain clear instructions for accessing such support.

Communications to Physicians

Respecting Physicians' Authority in Practicing Medicine

Healthcare providers, specifically physicians, play an essential role in safeguarding public health and ensuring that a patient is prescribed medication that is appropriate for that individual. Drug Watch can be a powerful tool for healthcare providers by providing the latest information on emerging drug safety issues in a central, easily accessible location.

In order to maximize the effectiveness of this website for physicians and other health care providers, it is essential that the Drug Watch website provide clear, accurate, useful and actionable information that a physician can use as an input in prescribing decisions. However, it is important to realize that the information on the Drug Watch website undoubtedly will be one of many inputs a physician will rely on in treating patients; other information likely used in prescribing decisions would be the medical history of the individual patient, the information contained on the drug label, the physician's experience with a specific drug, alternative treatment options available, etc. Consequently, it is critical that the FDA ensures that implementation of the Drug Watch website respects physicians' prescribing discretion and does not infringe on or usurp the physician's sovereign right to practice medicine. Given that Drug Watch will contain emerging safety information, about which FDA has not yet completed its analysis and about which it has not yet made a decision, it would be inappropriate for Drug Watch to attempt to persuade physicians to alter their medical practice based on Drug Watch. The purpose of Drug Watch should be to inform choice rather than to persuade.[14] To that end, Drug Watch should not advise patients or practitioners to discontinue prescriptions, and FDA must act with caution in advising physicians how to respond to information on the Drug Watch website.

[14] Ellen Peters (in press).

Furthermore, Drug Watch should make clear that the drug label remains the definitive document for purposes of the practice of medical care; the information contained in the label reflects careful evaluation of a drug's risks and benefits, while the information on Drug Watch reflects emerging information that the FDA is continuing to evaluate. As a result of the preliminary and inconclusive nature of the information on Drug Watch, FDA must ensure physicians understand that information contained on Drug Watch represents only additional information to consider and is not meant to supplant the information contained in the drug label. This is critical since the information on the Drug Watch website may not necessarily be consistent with the approved labeling of a drug. This inconsistency may, over the long term, erode the value of the label as the "definitive" product document, thereby depriving physicians of one definitive source to turn to for prescribing information. If physicians attempt to turn to a drug company's sales representatives to answer questions regarding this inconsistency, the sales representatives likely will be unable to clear up any confusion since they are constrained from discussing information that is not contained in the product label.

Providing Needed Information

In all instances, Drug Watch should provide fact-based information, as well as an assessment of the quality of the evidence surrounding emerging safety information. Providing such contextual information is important since as the Drug Watch guidance indicates, the "posting of information on the Drug Watch Web page does not mean that the FDA has concluded there is a causal relationship between the product and the risks or adverse events described" (lines 137-139) nor does it "mean the FDA is advising practitioners to discontinue prescribing the products that appear on the Drug Watch" (lines 139-140). Given these statements, it may be unclear to physicians how they should interpret Drug Watch postings, particularly in cases where the FDA has not evaluated the significance of the information.

This lack of clarity is exacerbated when the information posted for a drug does not contain the specificity necessary for judging how a risk may pertain to an individual patient. For example, the sample drug posting provided in the guidance (lines 85-88) fails to indicate how "elderly" is defined. It also fails to identify whether the risks potentially are linked to drug-drug interactions or other factors. Additionally, it neglects to provide a projected date for when the FDA's analysis of the risk signal is likely to be completed. Without more detailed information on the potential safety information, it is unlikely that physicians will know how to make use of the Drug Watch data in their treatment of individual patients.

Ensuring Timely Communication

It is extremely important for FDA to communicate clearly, frequently and accurately to physicians regarding Drug Watch, especially given that consumers will have access to the web site and may turn first to their personal physician for answers on how postings may affect them as individual patients. To that end, it is important for each posting on Drug Watch to list a point of contact at FDA with whom a physician may consult for more

information about a specific drug's potential safety risks. This is particularly critical during the interval in which the FDA considers the risk information as emerging and is still evaluating its relevance.

Communicating to Media

Many persons will initially hear about a new Drug Watch listing through the media. As FDA is well aware, the number of adverse event reports usually increases with media attention, thereby giving the impression that a safety issue is even more serious. We recommend that FDA plan ahead how it will deal with the media attention a new posting will garner, in order to dampen the social amplification of risk.

Communications About Entrepreneurial Use

As we believe the Agency has correctly pointed out, the listing of a drug on Drug Watch is not to be taken as an opportunity for competitor manufacturers whose similar drug is not on Drug Watch to improve marketing of its drug; nor is it to be diminished by the sponsor manufacturer in order to diminish the import of the potential safety issue. We strongly support this stance. Such practices would have the effect of implying a difference for which neither sponsor nor competitor drug is labeled. We recommend that FDA should enhance its vigilance on such false labeling, real or implied, and bring to bear against violators of this rule the full weight and force of its office. Each posting on Drug Watch should contain a strongly worded prohibition against entrepreneurial use, including inappropriate detailing. It also might be useful to have a statement on each Drug Watch listing that explicitly states to health care practitioners and patients that any company claiming that its product is safer than those appearing on Drug Watch is providing misleading information. We recommend that FDA include such a statement, along with a reminder to patients that they should not discontinue or switch any medication without further consulting their physician.

Accountability for Communications

FDA is taking a big step by reporting "emerging" information to the public without having a clear idea of how patients and doctors are likely to respond to such information. Anecdotal evidence on reactions to media coverage of alleged safety issues for certain drugs or drug classes (e.g., SSRIs) indicates that some patients become confused, afraid and stop taking needed medicines, and some doctors become frustrated and angry, not certain how to respond on behalf of their patients. We strongly recommend that FDA regularly monitor and evaluate the impact of communications on Drug Watch on patient and physician behavior, then modify communications appropriately so that patients are not unnecessarily frightened and physicians are not confused. We suggest that FDA use outside experts in medicine, psychology and risk communication to help it accomplish this crucial task.

Procedural Issues

Not withstanding the above remarks, we believe there may be an issue with respect to whether FDA has the legal authority to adopt Drug Watch in the manner proposed. Section 705 of the Federal Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. § 375, as well as the text and structure of the FDCA, suggest that FDA may be precluded from communicating unsubstantiated drug risk information as proposed in the draft Guidance. FDA has not addressed its legal authority in the draft Guidance and we believe it is important for it to do so.

At a minimum, however, a program such as Drug Watch must be adopted by FDA pursuant to notice- and- comment rulemaking under the Administrative Procedure Act ("APA"). Drug Watch constitutes a change in FDA's existing rules for addressing emerging risk information. Under settled principles of administrative law, agency action that effectively amends a previously adopted regulation, or that amends an agency's interpretation of a previously adopted regulation, triggers the APA requirement of notice-and-comment rulemaking. *See Alaska Prof. Hunters Ass'n, Inc. v. FAA,* 177 F.3d 1030, 1034 (D.C. Cir. 1999) ("When an agency has given its regulation a definitive interpretation, and later significantly revises that interpretation, the agency has in effect amended its rule, something it may not accomplish without notice and comment."). Here, FDA has said that, although it "has long provided information on drug risks and benefits to healthcare professional and patients . . . when we were certain of its significance or it prompted a regulatory action," the agency would henceforth "make important drug safety information available to health care professionals and patients" through the Drug Watch. 70 Fed. Reg. 24,606, 24,606 (May 10, 2005). The Agency may only lawfully accomplish this after notice-and-comment rulemaking.

Even if the Drug Watch does not effectively amend an agency regulation or interpretation, the program constitutes a legislative rule that can be issued only through notice-and-comment rulemaking. An agency may establish a binding norm with legal consequences for private parties or the agency only if it first follows these procedures. *See Croplife Am. v. EPA*, 329 F.3d 876, 883 (D.C. Cir. 2003) (a directive announced in a press release constitutes a substantive rule, for which notice-and-comment rulemaking is required, because it binds private parties or the agency itself with the force of law); *General Elec. Co. v. EPA*, 290 F.3d 377, 382-83 (D.C. Cir. 2002) (a "guidance" is a legislative rule because it purports to bind regulated entities and the agency); *see also Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1024 (D.C. Cir. 2000) (a guidance establishing a new regulatory regime constitutes a legislative rule for which notice-and-comment rulemaking is required). The draft Guidance commits FDA to specific actions and has profound consequences for regulated entities by changing the circumstances under which data they turn over to the Agency will be disclosed, with dramatic product liability and commercial implications. This is precisely the type of agency action that requires compliance with notice-and-comment rulemaking. The draft Guidance alters FDA's well-established regulatory regime for the dissemination of risk information. Accordingly, FDA may not lawfully adopt the Drug Watch through the publication of a Guidance Document.